UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,551	07/07/2006	Philip Buzby	NEN-22602/16	2072

37742 7590 05/13/2009

GIFFORD, KRASS, SPRINKLE, ANDERSON
& CITKOWSKI, P.C.
P.O. BOX 7021
TROY, MI 48007-7021

EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
05/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,551	BUZBY, PHILIP	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,13-16,18,21,23 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,13-16,18,21,23 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 10, 2009 has been entered.

Claims 1-7, 9, 10, 13-16, 18, 21, 23, and 26-30 are currently pending. In the response, Applicant amended claims 1 and 26.

The following are new grounds of rejection. Any previously made objections or rejections not reiterated below have been withdrawn in view of the amendment. Applicant's arguments filed on February 18, 2009 and resubmitted with the request for continued examination filed on March 10, 2009 that remain pertinent to the new grounds of rejection have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Provisional Application No. 60/481,443, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the disclosure of the '443 application does not provide adequate support for the methods recited in claims 4-6, 13, 15, 16, 29, and 30. The '443 application does not provide adequate support for the methods of claims 4 and 29, because it does not disclose adding an exonuclease, alkaline phosphatase, or a combination thereof to a purified reaction product (*i.e.* an amplification product treated with an inorganic pyrophosphatase or pyrophosphatase removing enzyme). The '443 application only discloses adding the exonuclease and/or alkaline phosphatase to an amplification product together with an inorganic pyrophosphatase or pyrophosphatase removing enzyme (see claims 35 and 42), and therefore, it does not provide adequate support for addition of an exonuclease and/or alkaline phosphatase after treatment with an inorganic pyrophosphatase as required by claims 4 and 29. The '443 application also does not provide adequate support for the methods of claims 5, 6, and 30, because it does not disclose conducting an enzyme inactivation step. The '443 application also does not provide adequate support for the method of claim 13, because it only discloses the use of a generic alkaline phosphatase or shrimp alkaline phosphatase (see

claims 35 and 42), and therefore, does not provide support for the use of bacterial alkaline phosphatase and/or calf intestinal alkaline phosphatase. Finally, the '443 application does not provide adequate support for the methods of claims 15 and 16, because it only discloses the use of an exonuclease (see claims 35 and 42), and therefore, does not provide adequate support for the use of the specific exonucleases recited in claims 15 and 16. Accordingly, claims 4-6, 13, 15, 16, 29, and 30 are not entitled to benefit of the earlier filing date of the '443 application, and therefore, these claims have an effective filing date of **September 30, 2004** (*i.e.* the filing date of the instant application).

Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The amendment to the specification filed on August 4, 2008 recites that the nucleic acid sequences appearing in Figure 1 are SEQ ID NO: 83-88. These sequences are not present in the Sequence Listing, which only has 64 sequences. Also, the amendment to the specification filed on February 18, 2009 recites that the nucleic acid sequences listed in Table 3 on pages 29-30 are SEQ ID NO: 65-82. These sequences are also not present in the Sequence Listing, which has only 64 sequences. Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 5, 6, 16, and 30 are rejected under 35 U.S.C. 102(a) as being anticipated by Xiao et al. (Genome Research (published online August 12, 2004) 14: 1749-1755; newly cited).

As noted above in section 2, the instant claims 5, 6, 16, and 30 have an effective filing date of September 30, 2004. Therefore, the Xiao reference qualifies as prior art under 35 U.S.C. 102(a).

These claims are drawn to a method of improving single base extension reactions by treating an amplification product to be used in the single base extension reaction with an inorganic pyrophosphatase or a pyrophosphate removing enzyme.

Regarding claims 5, 6, and 30, Xiao teaches a method for inhibiting misincorporation of a terminator in a single base primer extension reaction, comprising:

(a) amplifying a nucleic acid template in the absence of an inorganic pyrophosphatase to yield a nucleic acid synthesis product comprising a nucleic acid amplification product and a quantity of inorganic pyrophosphate (page 1754, column 2),

(b) incubating the nucleic acid synthesis product with an inorganic pyrophosphatase, an exonuclease, and an alkaline phosphatase under conditions sufficient to decrease the quantity of pyrophosphate and degrade residual nucleotides and unextended primers to yield a purified reaction product (page 1754, column 2),

(c) inactivating the enzymes (page 1754, column 2),

(d) combining the purified reaction product, a primer, a terminator having a detectable label, and a polymerase to form a mixture (page 1754, column 2; page 1754, column 1 provides further description of the TDI cocktail), and

(e) incubating the mixture under conditions sufficient to extend the primer by the addition of the terminator in a single base primer extension reaction (page 1754, column 2), wherein decreasing the quantity of inorganic pyrophosphate in the nucleic acid synthesis product inhibits pyrophosphorolysis in the single base primer extension reaction, thereby inhibiting misincorporation of a terminator (see abstract, pages 1750-1751, and page 1753).

Regarding claim 16, Xiao teaches the use of exonuclease I (page 1754, column 2).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-7, 9, 10, 13-16, 21, and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. (US 6,180,408 B1; cited previously) as evidenced by Grazinoli-Garrido & Sola-Penna (Annals of the Brazilian Academy of Sciences (2004) 76(4): 699-705; newly cited) and as evidenced by Richter & Schafer (European Journal of Biochemistry (1992) 209: 343-349; newly cited) in view of Vander Horn et al. (BioTechniques (1997) 22: 758-765; cited on an IDS).

These claims are drawn to methods of inhibiting misincorporation of a terminator nucleotide in a single base extension reaction. The methods comprise treating a nucleic acid synthesis product with an inorganic pyrophosphatase or a pyrophosphate removing enzyme to degrade inorganic pyrophosphate and thereby reduce the occurrence of pyrophosphorolysis.

Kwok teaches a homogenous genotyping method comprising PCR amplification, single base extension, and fluorescence polarization detection (see abstract, column 6, line 55 – column 7, line 10, and Figure 2 for a general description).

Regarding claims 1 and 26, the method of Kwok comprises:

(a) amplifying a nucleic acid template in the absence of inorganic pyrophosphatase to yield a product of a nucleic acid synthesis reaction comprising an amplification product and a quantity of inorganic pyrophosphate (column 10, lines 29-47, where the PCR amplification step inherently generates inorganic pyrophosphate)

(b) purifying the nucleic acid synthesis reaction product to obtain a purified reaction product (column 10, lines 48-58, where the nucleic acid synthesis product is treated with exonuclease I and shrimp alkaline phosphatase to degrade residual primers and nucleotides)

(c) combining the purified reaction product with a primer, a labeled terminator nucleoside, and a polymerase (column 10, line 60 - column 11, line 2)

(d) extending the primer by addition of the labeled terminator in a single base extension reaction (column 11, lines 2-5).

Regarding claims 2 and 27, the PCR amplification product obtained in the method of Kwok contains residual primers and nucleotides (see column 10, lines 48-58).

Regarding claims 3, 5, and 28, Kwok teaches incubating the nucleic acid synthesis product with an exonuclease and an alkaline phosphatase to degrade the residual primers and nucleotides and then inactivating the enzymes by heating the sample to 95°C (column 10, lines 48-58).

Regarding claim 7, Kwok teaches that the detectable label is a fluorescent label (see column 10, line 67 and column 11, lines 9-55).

Regarding claims 9 and 10, Kwok teaches detecting the label using fluorescence polarization (column 11, lines 9-55).

Regarding claim 13, Kwok teaches that the alkaline phosphatase is a bacterial alkaline phosphatase (see column 6, lines 63-64, where HK thermolabile phosphatase is a bacterial alkaline phosphatase).

Regarding claim 14, Kwok teaches that the alkaline phosphatase is shrimp alkaline phosphatase (column 10, line 51).

Regarding claims 15 and 16, Kwok teaches that the exonuclease is exonuclease I or mung bean exonuclease (see column 6, lines 60-62 and column 10, line 52).

Regarding claim 21, Kwok teaches that the steps are performed in a single reaction container (see Example 5 at column 12, lines 40-67).

Kwok does not teach incubating the nucleic acid synthesis product with an inorganic pyrophosphatase or a pyrophosphate removing enzyme to reduce the quantity of inorganic pyrophosphate present in the nucleic acid synthesis product and thereby produce a purified reaction product as required by independent claims 1 and 26.

Vander Horn teaches a method for conducting cycle sequencing using a mixture comprising a thermostable DNA polymerase and a thermostable inorganic pyrophosphatase (see abstract, pages 758-760, and page 762). Vander Horn teaches that the mixture of Thermo Sequenase and inorganic pyrophosphatase produces highly accurate cycle sequencing results (see abstract, page 762, and page 764). Vander Horn also teaches that the thermostable DNA polymerase, Thermo Sequenase, incorporates ddNTPs at an efficiency several thousand-fold higher than other thermostable DNA polymerases, thereby reducing the amount of costly ddNTPs required to conduct the reaction and also reducing the likelihood of erroneous results stemming from inefficient terminator incorporation (see abstract, page 762, and page 764). Vander Horn further teaches that Thermo Sequenase also catalyzes pyrophosphorolysis at dideoxy termini, and therefore, sequencing reactions conducted using this enzyme should also include a thermostable inorganic pyrophosphatase to counteract this undesirable effect (see abstract and page 762).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Vander Horn to the method of Kwok. An ordinary artisan would have been motivated to substitute the Thermo Sequenase DNA polymerase taught by Vander Horn for the AmpliTaq DNA polymerase taught by Kwok when conducting the single base extension reaction of Kwok, since Vander Horn taught that the Thermo Sequenase enzyme incorporated ddNTPs very efficiently, thereby reducing the amount of costly ddNTPs required to conduct the reaction and reducing the likelihood of erroneous results stemming from inefficient terminator incorporation (see abstract, page 762, and page 764). An ordinary artisan practicing the single base extension reaction of Kwok would have expected the same benefits disclosed by

Vander Horn when substituting the Thermo Sequenase for AmpliTaq, since both methods utilized fluorescently labeled ddNTPs. Therefore, the ordinary artisan would have had a reasonable expectation of success in applying the teachings of Vander Horn to the method of Kwok. An ordinary artisan also would have been motivated to include an inorganic pyrophosphatase in the single base extension reaction of Kwok, since Vander Horn taught that the inclusion of this enzyme was necessary to counteract pyrophosphorolysis stimulated by the Thermo Sequenase enzyme (see abstract and page 762). Conducting the single base extension reaction in the presence of an inorganic pyrophosphatase as suggested by the teachings of Vander Horn would result in the production of a purified amplification reaction product as required by claims 1 and 26. It is noted that the broadest reasonable interpretation of claims 1 and 26 does not exclude methods wherein the production of a purified reaction product and the formation of a mixture comprising the purified reaction product, a DNA polymerase, a labeled terminator, and a primer occurs simultaneously (*i.e.* the method suggested by the combined teachings of Kwok and Vander Horn).

Regarding claims 4 and 29, it would have been *prima facie* obvious to add the exonuclease and alkaline phosphatase to the amplification product after the addition of inorganic pyrophosphatase, since section 2144.04 IV C of the MPEP states that any order of mixing ingredients is *prima facie* obvious. In this case, there is no particular reason for adding inorganic pyrophosphatase to the amplification product before the addition of shrimp alkaline phosphatase and exonuclease I as required by claims 4 and 29 or after treatment with shrimp alkaline phosphatase and exonuclease I as taught by Vander Horn, and no evidence has been presented to suggest that unexpected results are associated with the claimed order of mixing ingredients.

Therefore, the claimed order of mixing ingredients is *prima facie* obvious in the absence of secondary considerations.

Finally, regarding claims 6 and 30, including inorganic pyrophosphatase as suggested by the teachings of Vander Horn in the method of Kwok would inherently result in inactivation of the enzyme during the method. Kwok teaches embodiments of the method wherein the completed single base extension reaction is diluted with methanol prior to measuring fluorescence polarization (see Example 7 at column 14, lines 35-66). In these embodiments of the method resulting from the combined teachings of Kwok and Vander Horn, the addition of methanol inherently results in inactivation of the inorganic pyrophosphatase, as evidenced by the teachings of Richter & Schafer and the teachings of Grazinoli-Garrido & Solla-Penna (see page 348 of Richter & Schafer and pages 699-703, especially Figure 1 of Grazinoli-Garrido & Solla-Penna). Thus, in the absence of any secondary considerations, the methods of claims 1-7, 9, 10, 13-16, 21, and 26-30 are *prima facie* obvious over Kwok in view of Vander Horn as evidenced by Grazinoli-Garrido & Solla-Penna and Richter & Schafer.

8. Claims 18 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. (US 6,180,408 B1; cited previously) as evidenced by Grazinoli-Garrido & Sola-Penna (Annals of the Brazilian Academy of Sciences (2004) 76(4): 699-705; newly cited) and as evidenced by Richter & Schafer (European Journal of Biochemistry (1992) 209: 343-349; newly cited) in view of Vander Horn et al. (BioTechniques (1997) 22: 758-765; cited on an IDS) and further in view of Jack et al. (WO 01/23411 A2; cited previously).

These claims are drawn to the method of claim 1, wherein the terminator is an acyclo nucleoside terminator and the method is conducted using a polymerase that has a higher affinity for an acyclo nucleoside terminator than for a dideoxy terminator.

The combined teachings of Kwok and Vander Horn as evidenced by Grazinoli-Garrido & Solla-Penna and Richter & Schafer result in the methods of claims 1-7, 9, 10, 13-16, 21, and 26-30, as discussed above.

These references do not teach that the terminator is an acyclo nucleoside terminator and the method is conducted using a polymerase that has a higher affinity for an acyclo nucleoside terminator than for a dideoxy terminator.

Jack teaches methods and compositions for improving the incorporation of chain terminating nucleotides by DNA polymerases (see abstract and page 9, line 30 - page 10, line 10). Regarding claims 18 and 23, Jack teaches that dye-labeled acyclo-NTPs are more readily incorporated by Family B archaeon DNA polymerases, such as Vent, Pfu, Deep Vent, and 9N, than dye-labeled ddNTPs (page 18, line 9 – page 19, line 14). Jack also teaches that increasing the efficiency of nucleotide terminator incorporation reduces costs, decreases background, and increases assay sensitivity (page 25, line 31 - page 26, line 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Jack to the method resulting from the combined teachings of Kwok and Vander Horn. An ordinary artisan would have been motivated to substitute dye-labeled acyclo NTPs and a Family B archaeon DNA polymerase for the dye-labeled ddNTPs and AmpliTaq-FS taught by Kwok, since Jack taught that dye-labeled acyclo NTPs were more efficiently incorporated by a Family B archaeon DNA polymerase than ddNTPs (page 18, line 9

- page 19, line 14). Since Jack taught the more efficient terminator incorporation reduced costs, decreased background, and improved sensitivity (page 25, line 31 - page 26, line 2), an ordinary artisan would have been particularly motivated to substitute dye-labeled acyclo NTPs and a Family B archaeon DNA polymerase in the method of Kwok in order to obtain these advantages. An ordinary artisan would have had a reasonable expectation of success in using dye-labeled acyclo NTPs and a Family B DNA polymerase in the method of Kwok, since Jack taught that they were suitable for single base extension methods, such as the single base extension method taught by Kwok (page 26, line 25 – page 27, line 2). Thus, the methods of claims 18 and 23 are *prima facie* obvious over the cited references in the absence of secondary considerations.

Response to Arguments

9. Applicant's response does not appear to address the issue of compliance with the sequence rules. As noted above, the identification of the nucleic acid sequences appearing in the specification and drawings as SEQ ID NO: 65-88 results in a failure of the application to comply with the sequence rules, because the sequence listing only contains SEQ ID NO: 1-64. Submission of a substitute sequence listing containing 88 sequences or correction of the specification so that the recited sequences are identified by one of SEQ ID NO: 1-64 as appropriate should correct this problem.

As noted above, the previously made rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of Tabor and the rejection of claims 18 and 23 under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of Tabor and further in view of Jack have been withdrawn in view of the claim amendments. Some of

Applicant's arguments filed on February 18, 2009 and resubmitted on March 10, 2009 with the request for continued examination remain pertinent to the new grounds of rejection presented above. These arguments have been fully considered, but they were not persuasive.

Applicant first argues that Kwok does not teach the claimed step of producing a purified reaction product (see page 10). This argument was not persuasive, because the rejection is based on the combined teachings of the Kwok and Vander Horn. As discussed above, the teachings of Vander Horn would have suggested to an ordinary artisan practicing the method taught by Kwok that treating the amplification product with inorganic pyrophosphatase prior to conducting the subsequent single base extension reaction would provide the useful benefit of reducing inaccuracies resulting from pyrophosphorolysis. Treatment of the amplification product produced in the method of Kwok with an inorganic pyrophosphatase, as suggested by the teachings of Vander Horn, would result in the production of a purified reaction product as required by independent claims 1 and 26.

Applicant also argues that Kwok does not teach conducting the method in a single tube as required by claim 21 (see pages 10 and 15). This argument was not persuasive, because Kwok teaches this limitation (see Example 5 at column 12, lines 40-67).

Finally, Applicant argues that the cited references do not teach or suggest inactivation of the inorganic pyrophosphatase as required by claims 6 and 30. This argument was not persuasive, because as discussed above, adding an inorganic pyrophosphatase simultaneously with or prior to the addition of Exonuclease I and shrimp alkaline phosphatase, as suggested by the teachings of Vander Horn, and conducting the remaining steps of the method taught by Kwok (*i.e.* single base extension using fluorescently labeled terminators, dilution of the reaction

mixture with methanol, and measuring fluorescence polarization) would inherently result in inactivation of the inorganic pyrophosphatase. As discussed above, the dilution of the completed single base extension reaction with methanol as taught by Kwok in Example 7 would inherently result in the inactivation of the inorganic pyrophosphatase as evidenced by the teachings of Grazinoli-Garrido & Solla-Penna and Richter & Schafer. It is also noted that the claims as written do not require the pyrophosphatase inactivation step to occur at a particular time in the method (*e.g.* prior to conducting the single base extension reaction), and therefore, inactivation at the conclusion of the single base extension reaction is not excluded by the instant claims.

Applicant's remaining arguments have been considered, but they are moot in view of the new grounds of rejection presented above.

Conclusion

10. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

amb